Comments

Line 188: Please make clarify why '7 days' are shown as an example in parenthesis. Is there any possibility to permit conducting the study for longer days than 7 days? In that case, additional toxicology study is required? Please describe how to determine the duration of dosing, what factor should be considered when determining it.

Line 230-231: In case of a use of novel excipient in exploratory IND study, this draft guidance is recommended that the safety should be appropriately qualified according to draft guidance on Nonclinical Studies for Development of Pharmaceutical Excipients, and it seems that more toxicological information are required as compared those of candidates. We think that the novel excipient is safe, if the 2-week repeated dose toxicity studies using the formulation including the novel excipient are conducted and the genotoxicity studies of a novel excipient itself are evaluated, without conducting the reproductive and local toxicity studies. Can we carry out exploratory IND study by such a view? Furthermore, when the approved excipient is used exceeding a maximum amount, we think that the amount used is safe, if the 2-week repeated dose toxicity studies using the formulation including the excipient are conducted only. Can we carry out exploratory IND study by such a view?

Line 308-332, 388-424: It will be more helpful if schemes like the attachment are prepared for Sections C.1. and C.3.

Line 310-311: This definition might be too strict. Recently pharmacological potentials of novel candidates would be getting high, it means the expected pharmacological doses would be lower. If we define a microdose as less than 1/100th of the dose calculated to yield a pharmacological effect of a test substance and a maximum dose of <100micrograms, few of substances would be applicable to the category.

Line 317-320: If in vitro metabolism studies are not done by this stage, it should be described which toxic studies are required instead of the extended single dose in 1 species. It is considered that in vitro metabolic profile study is not always done by this stage. In principle, description in this section should be consistent with attachment.

Line 318-319, 342-343: In part A, a species justified by in vitro metabolism data and by comparative data on in vitro pharmacodynamic effects is recommended as to European CPMP, otherwise, in part B, a sensitive species accompanied by toxicokinetic evaluations is recommended. I can't imagine the most important point to chose a testing species. I suppose the selection rationale of species might be it depends on dosing range. Please make clear this point.

Line 320-321: For almost all of the imaging studies using PET, the route of exposure in human must be intravenous. The route of exposure in animals should be intravenous regardless of the intended clinical route.

Line: 324 to 326: In EMEA position paper (CPMP/SWP/2599/02Rev1, 23 June 2004), a safety factor of 1000 is recommended to set the limit dose. This discrepancy between FDA and EMEA should be rethought for harmonization.

Line 330-332: Scientific evidence to show that genetic toxicology testing is not needed because of single microdose exposures and routine environmental exposures is not clear. It would be more helpful for understanding the policy of this guidance if appropriate references were cited.

Line 380-385: If we can confirm pharmacological effects and also dose limiting adverse effects using the doses less than the proposed stopping dose, can we proceed to phase 2 studies without some traditional phase 1 studies?

Line 404: Please define "frank toxicity".

Line 448-449: The original text should be revised to “Toxicology study in nonrodent species with the same dosing schedule at NOAEL dose, at maximum, in the rodent 2-week toxicology study”, in order to clarify and keep consistency with the description in Section C.2.